Monitoring of a diabetic patient

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Monitoring patients with diabetes mellitus

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The primary goals of therapy are to eliminate the clinical signs of diabetes while preventing short-term complications (hypoglycemia, DKA). Concurrent problems also need to be controlled, as they may render glycemic control difficult. The monitoring techniques are similar for dogs and cats. Different to dogs, however, cats may develop relevant stress hyperglycemia when brought to an unfamiliar environment and/or manipulated by a veterinarian. Stress hyperglycemia may render the interpretation of blood glucose concentrations and blood glucose curves, generated in the hospital, difficult. Measurement of blood glucose at home is less stressful or even stress-free when done by experienced owners and results of home-monitoring are usually more reliable than results generated in the hospital (Reusch 2015). Another important difference between dogs and cats is the fact, that a substantial percentage of cats may experience diabetic remission, whereas remission is rare in dogs and usually only occurs after castration of a bitch with diestrus-associated diabetes. Diabetes remission is considered to be one of the major treatment goals in diabetic cats by some authors (Bloom and Rand 2014); the most recent guidelines on feline diabetes, however, do not list remission as a major treatment goal (Sparkes et al 2015).

In dogs cataract formation is inevitable in most dogs, as many as 80% of dogs will develop cataracts within 16 months of diagnosis (Beam et al 1999). Cataract formation may be delayed with good glycemic control and avoidance of wide fluctuations of blood glucose (Nelson 2015).

Management of a diabetic pet may be stressful for owners and may impair their own quality of life. Recent survey revealed areas with the most negative impact, such as “difficulties leaving dog/cat with family or friends”, “boarding difficulties” “vision (dog)”, “hypoglycemia”, “work life”, “social life”, “costs”, “wanting more control” (Niessen et al 2010, 2012). It is, therefore, advisable to discuss with every single owner his/her biggest worries and curtail the treatment and monitoring plan accordingly. For instance, if hypoglycemia is the biggest worry one should avoid aggressive treatment protocols, if costs are a major concern it may be necessary to simplify the treatment, if more control is desired home-monitoring should be introduced (Sparkes et al 2015).

Newly diagnosed diabetic animals should be monitored more frequently than established and stable diabetics. Initially, weekly re-checks are recommended, with improving glycemic control time intervals can be prolonged. The first 3 months is the most important time in the life of a diabetic pet due to several reasons: owner needs support to get familiar with the new challenges, diabetic remission may occur requiring reduction and cessation of insulin application, insulin resistance may become obvious requiring further work-up.

History and physical examination

The most important parameters to assess glycemic control are the clinical signs observed by the owner, the stability of the body weight and the findings during physical examination. Dogs and cats, in which the initial clinical signs (e.g. pu/pd, polyphagia, lethargy, poor hair coat) have resolved, the body weight stays within the desired range and physical examination reveals a good clinical condition, are usually well controlled. Weight gain above the desired range points to insulin overdose; in cats with poor glycemic control weight gain should raise the suspicion for hypersomatotropism. Measurement of serum fructosamine concentration and generation of blood glucose curves will help to confirm the status of good or poor glycemic control, blood glucose curves are particularly useful for the “fine-tuning” of insulin therapy. Measurement of blood glucose will help to detect periods of hypoglycemia which may go otherwise unnoticed; increasing the insulin dose only on the basis of clinical signs may therefore be problematic. Blood glucose measurements will also help to determine if diabetic remission has occurred. Clinical signs are usually well controlled if most blood glucose concentrations are approximately between 4.5 and 15 mmol/l throughout 24 hours. In cats, however, clinical signs may not always

match blood glucose concentrations, e.g. the cat may appear clinically much better than one would assume looking at the blood glucose levels (Norworthy and Wexler-Mitchell 2015).

Serum fructosamine concentration

Fructosamine is the product of an irreversible reaction between glucose and the amino groups of plasma proteins. Its concentration mainly depends on the blood glucose concentration (e.g. extent and duration of hyperglycemia) and the lifespan of plasma proteins; it is generally assumed that fructosamine reflects the mean blood glucose concentration of the preceding 1–2 (-3) weeks. The reference ranges differ slightly between laboratories but are usually between approximately 200 and 360 μmol/l. Fructosamine is higher in male than in female cats and lean cats have lower fructosamine than normal weight and obese cats (Gilor et al 2010). In the vast majority of newly diagnosed diabetic dogs and cats, fructosamine levels are > 400 μmol/l and may be as high as 1500 μmol/l. Fructosamine is not affected by short-term changes in blood glucose concentration and thus is usually normal in cats with stress hyperglycemia (Reusch et al 1993, Lutz et al 1995, Crenshaw et al 1996). However, in animals with a very recent onset of diabetes or with mild diabetes, serum fructosamine may be in the normal range, rendering the differentiation between stress and diabetic hyperglycemia impossible. In a recent study, two groups of healthy cats were infused with glucose to maintain either a marked or a moderate hyperglycemia (30 mmol/l or 17 mmol/l) for 42 days. In the group with marked hyperglycemia, it took 3 – 5 days until fructosamine exceeded the upper limit of the reference range, in the group with moderate hyperglycemia fructosamine concentrations mostly fluctuated just below the upper limit of the reference range (Link and Rand 2008). Of note, fructosamine is influenced by hypoproteinemia/hypoalbuminemia (decrease), hyperlipidemia (decrease, dogs), azotemia (decrease, dogs), hyperthyroidism (decrease), hypothyroidism (increase) and paraproteinemia (increase) (Reusch and Tomsa 1999, Graham et al 1999, Reusch and Haberer 2001, Reusch et al 2002, Zeugswetter et al 2010). In those circumstances, fructosamine should not be used to monitor glycemic control.

After initiating insulin therapy, blood glucose concentrations usually start to decrease which is followed by a decrease in fructosamine after a few days. Generally, fructosamine concentrations increase when glycemic control worsens and decrease when glycemic control improves. We consider 50 μmol/l to be the so-called critical difference between consecutive measurements; a recent study found a lower critical difference of 33 μmol/l (Link and Rand 2008). Fructosamine is not affected by stress nor by lack of food intake, both are common in case of hospitalization. Routine measurement of fructosamine is therefore helpful to clarify the effects of stress or lack of food intake, generally spoken to clarify discrepancies between history and physical examination and blood glucose measurements. Most well-controlled diabetic pets are slightly hyperglycemic for some time during a 24-hour period and consequently, fructosamine will not become completely normal. In cats which achieve diabetic remission, however, fructosamine concentrations decrease into the normal range. As long as fructosamine is elevated (even if only slightly), the diabetes is not in remission. Fructosamine between approximately 350 and 450 μmol/l reflects good glycemic control, concentrations between 450 and 550 μmol/l suggest moderate and concentrations above 550 – 600 μmol/l poor glycemic control. In the latter situation, fructosamine is not helpful to identify the underlying problem because the various possible reasons for poor regulation (e.g. application error, insulin underdose, too short duration of insulin effect, diseases causing insulin resistance, Somogyi phenomenon) are associated with high blood glucose concentrations. Fructosamine in the lower half of the reference interval (< 300 μmol/l) suggests prolonged periods of hypoglycemia and/or diabetic remission or a concurrent problem causing a decrease in fructosamine. The ranges should be considered as a rough guideline, as there are substantial differences in glycation between individuals (Link and Rand 2008). Fructosamine is useful if followed in individual patients over time, however, it should never be used as the sole indicator of the quality of metabolic control. The parameter is

less important than the evaluation of clinical signs and body weight and generation of blood glucose curves. Shipping of sample for fructosamine measurement should be on cold packs if samples will be in transit for more than 24 hours.

Urine glucose monitoring

Glucose is freely filtered by the glomerulus and reabsorbed in the proximal tubules by the sodium-glucose cotransporter 2 (SGLT2). When the blood glucose concentration exceeds the so-called renal threshold (dogs approx. 12 – 12 mmol/l, cats approx. 15 – 17 mmol/l), glucose is excreted in the urine. The higher the blood glucose concentration is, the more glucose is found in the urine, which would in theory render the urine test a valuable monitoring tool. However, measurement of urine glucose may be misleading for several reasons: 1) the result does not reflect the actual blood glucose concentration, but is an average over the time of urine accumulation in the bladder, 2) a negative urine test does not differentiate between hypoglycemia, normoglycemia or mild hyperglycemia, 3) hydration status and urine concentration may affect the result. 4) It is known from human diabetics that renal glucose excretion varies considerably between patients and also within the same patient. It has been suggested to re-evaluate the concept of renal glucose threshold (Pickup 2003, Rave et al 2006, Wolf et al 2009). We strongly discourage owners to adjust the insulin dose on the basis of morning urine glucose measurements. Owners, who are unable to measure blood glucose but still want to do some type of monitoring, may be advised to use urine glucose measurements in all urine samples voided throughout one day per week. Persistent glycosuria would suggest inadequate glycemic control and the need for thorough evaluation in the hospital. If no glucose is detected in any of the samples, the pet is either very well controlled, in diabetic remission or is overdosed with insulin and should also be evaluated by a veterinarian. In dogs and cats prone to develop DKA, monitoring of urine ketone bodies may be helpful.

Blood glucose measurements and blood glucose curves

Generally, a single blood glucose concentration is helpful only if hypoglycemia is identified. Determination of blood glucose at the time of assumed glucose nadir is also unreliable, as time of nadir varies between animals and also within the same animal. Next to clinical signs serial measurements of blood glucose throughout the day (BGC) is the most important monitoring tool for diabetic dogs and cats. Ideally, BGCs are generated at home (HM) to avoid the influence of stress and lack of food intake on glucose measurements. Glucose should be measured before the insulin injection and every 2 hours thereafter until the next insulin injection is due, in case of suspected hypoglycemia measurement every hour may be required. If the glucose nadir is not reached during this time, insulin application should be delayed and glucose measurements should be continued. If a BGC is generated in the hospital the owner should give insulin and food at home and bring the animal to the hospital as soon as possible. Only glucometers validated for the dog and cat by an independent study should be used. Many glucometers designed for humans are plasma-calibrated and as the glucose content of erythrocytes differ markedly between pets and humans, those devices usually underestimate the glucose concentration in pets.

Opinions on the question, how often owners should check their pet's blood glucose, differ. Some investigators have suggested that in cats measurements should be performed several times per day and adjust the insulin dose accordingly following a very tight dosing algorithm. Those algorithms are sometimes called “remission protocols” and it has been claimed that following those protocols leads to higher remission rates (Roomp and Rand 2009, Roomp and Rand 2012). However, those intensive protocols require owners who have the time to measure several times per day and they bear a high risk of hypoglycemia, even when performed under close supervision. The recent ISFM guidelines do not recommend those protocols (Sparkes et al 2015). Our protocol in Zurich foresees that owners generate a BGC once a week during the first

months of therapy and generally 5-7 days after any adjustment in insulin dose. After stabilization (and if no remission is achieved in cats), the time intervals are prolonged to approximately every 3 to 4 weeks. We also ask owners to measure the fasting blood glucose (pre-insulin glucose) twice weekly and to perform a spot glucose check whenever they feel uncertain about the well-being of the cat. Although many of our owners work full-time, this protocol is feasible for most of them, as they generate the BGC during the weekend. There are cases in which we ask for additional BGCs (e.g. in an extremely unstable diabetic), but those are rare exceptions. Most owners appreciate the fact, that they have more control over the disease by performing HM, for a minority, however, HM may be an additional burden (Kley et al 2004).
BGCs are extremely helpful for the titration of the insulin dose, either upwards or downwards. BGCs are assessed by evaluating the pre-insulin glucose, glucose nadir, duration of effect and degree of glucose fluctuations. The highest glucose concentration, which is usually (but not always) the fasting/pre-insulin concentration should not exceed 10 – 15 mmol/l, the nadir should ideally be between 4.5 – 7.8 mmol/l. Lower nadirs may be due to insulin overdose (including sudden improvement of insulin-resistant states), excessive overlap of insulin actions or lack of food intake. They may also be found in cats in which diabetes is ready to go into remission or is already in remission. Finding a nadir below 70 mg/dl (3.9 mmol/l) should always lead to a reduction of the insulin dose. Dose changes are usually made in steps of 0.5 (-1.0) U in cats and in steps of 10-20% in dogs. The duration of effect is defined as the time from the insulin injection through the glucose nadir until the blood glucose concentration exceeds 10 – 15 mmol/l, it should be evaluated when the glucose nadir is within the target range and be ideally approximately 12 hours. If the duration is less than 8 – 10 hours, the patient usually reveals signs of diabetes, and if duration is longer than 14 hours the risk of hypoglycemia or the occurrence of the Somogyi effect increases. If those findings are persistent, a switch to a longer respectively shorter acting insulin should be made. Remission is defined as the situation in which the clinical signs of diabetes have resolved, serum fructosamine and blood glucose concentration are in the normal range and insulin therapy can be ceased. In cats in which all blood glucose measurements of a BGC range between 4.5 – 6.7 mmol/l and serum fructosamine concentration is < 350 µmol/l we start to reduce the insulin dose in steps of 0.5 U/cat BID every 5 – 7 days. The owner is advised to monitor the cat closely with regard to re-appearance of clinical signs and a BGC is performed prior to each reduction step. The insulin is reduced until a dose of 0.5 U/cat BID is reached; if the blood glucose is still normal, insulin administration is terminated. Close clinical monitoring and regular glucose measurement (e.g. fasting blood glucose twice per week) is recommended to ensure that there is no relapse of the disease. Reduction is done in larger steps than 0.5 U/cat if hypoglycemia is seen.
It is important to realize, that BGCs can vary markedly from day to day, even when they are generated at home (Fleeman and Rand 2003, Alt et al 2007). It has been shown, that in cats with good glycemic control variability between BGCs is less than in cats with moderate or poor glycemic control (Alt et al 2007). One of the major advantages of home monitoring is that the veterinarian can ask the owner for more than one BGC before a treatment decision is made. This is of particular importance in pets that are difficult to regulate. Treatment decisions should never be made on the basis of BGCs alone, but should always include the interpretation of the clinical situation.

Continuous glucose monitoring

CGM systems measure interstitial fluid glucose concentrations and usually record the glucose concentration every 5 minutes. Systems such as the Guardian REAL-Time (Medronic) and the Dexcom G4 are useful for diabetic patients that are hospitalized for several days (e.g.in case of DKA). Transmission of data is wireless and only possible if the monitor is within 2-3 meters of the patient, therefore they are not suitable for HM. In contrast, the CGMS iPro2 (Medtronic) records glucose values for up to 7 days without displaying the data on a monitor; instead, at the end of the monitoring period, the data are uploaded on a computer and evaluated

retrospectively. Because the iPro2 does not involve a monitor, it can be used in the home environment and may be particularly useful in difficult to regulate diabetes pets (Salesov et al, submitted).

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